Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendments, claims 28-60 are pending in the application, with claims 28-31 being the independent claims. Claims 28-31 have been amended to clarify Applicants' claimed invention by specifically stating the "each of said one or more biological target molecules is a receptor protein." Support for the amendment of claims 28-31 can be found, *inter alia*, at page 12, lines 21-30, of the application as filed. Claim 45 has been amended to correct a typographical error. In claim 45, the word "receipt" has been deleted and the word "receptor" inserted therefore. Support for this amendment can be found, *inter alia*, in the specification at page 20, lines 4-13, and in claim 13, of the application as filed. These changes are believed to introduce no new matter and, their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claim 45 under 35 U.S.C. § 112, second paragraph, as being indefinite. Office Action, section 3, lines 1-3. Applicants respectfully traverse this rejection.

Specifically the Examiner states that "[c]laim 45 is rejected over the recitation of the phrase, 'receipt'. It is not clear what kind of receipt is claimed. Is the KDR receptor claimed or a new biochemical named KDR receipt is claimed or both are claimed? The metes and bounds of the claim is vague and indefinite." Office Action, section 2, lines 4-6.

Claim 45 has been amended to delete the work "receipt" and to insert the word "receptor" therefore. Applicants respectfully submit that the Examiner's rejection of claim 45 under 35 U.S.C. § 112, second paragraph, has been accommodated and should be withdrawn.

II. Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 28-42, 44, 46, 49, 50, 53, 55, 56, and 58-60 under 35 U.S.C. § 102(b) as being anticipated by Foulkes et al. (PCT international Publication number WO 92/13063) (August 6, 1992). Office Action, section 5, lines 1-3. Applicants respectfully traverse this rejection.

Specifically, the Examiner is of the opinion that:

> Foulkes et al teach a process for determining the pharmacological effect of a substance on the activity of various biological target molecules, wherein a substance is applied to test cells which contain one or more biological target molecules and the effect of the substance on the activity of the target molecules is determined, characterized in that test cells are derived or not derived from one type of tissues and one species (Claims 67-72 and 104 and Page 56, line 5 to page 61, line 20) and
>
> a) a defined amount of a test substance is applied to test cells which differ in that they contain one or more different biological target molecules (Claims 67-72 and Claims 92-102 and page 56, Addition of chemicals to cells Subsection); and
>
> [i]) the effect of the substance on the or each biological target molecule is measured using a detection system coupled to the activation

of the target molecule (Claims 94-103 and Page 57, line 5 to page 58, line 8); and/or

ii) the effect of the substance on different regulatory mechanisms triggered by the activation of the target molecule is determined by measuring the effects using a plurality of detection systems each coupled to the different regulatory mechanisms, and the effects of the test substance on the different test cells or the effects determined using different detection methods are directly compared with one another (Figure 20 and Page 58, line 13 to page 59, line 12).

(Office Action, section 5, lines 4-20).

The Examiner is further of the opinion that:

Foulkes et al teach a process characterized in that a plurality of substances, optionally in several dilutions, are applied in parallel to one or more sets of cellular substrates, each set constituting a group of different assays or assay formats based on the same targeting cell (Claims 84-87 and page 56, Addition of chemicals to cells Subsection).

Foulkes et al teach a process characterized in that the test cells are mammalian and human cells (Claims 76-79 and Page 42, line 5 to page 43, line 11).

Foulkes et al teach a process characterized in that the test cells contain a reporter gene under the control of a regulatory sequence which responds to the change in the concentration of a messenger substance of a signal transmission pathway, of which the target molecule is a component, and that the effect of the test substance on the target molecule is determined in a change in the expression of the reporter gene (Figures 1-4, 6-9 and 11-12 and Page 57, line 5 to page 58, line 8 and Figures 20-24).

Foulkes et al teach a process characterized in that the reporter gene is luciferase (Figures 1-4, 6-9 and 11-12 and Page 57, line 5 to page 58, line 8).

Foulkes et al teach a process characterized in that the test cells which are dependent on a growth factor for their proliferation are cultivated in the presence of the growth factor and the effect of the substance on the cells is determined by indirectly measuring the apoptosis or the proliferation of the cells (Page 2, line 23 to page 5, line 5 and Page 42, line 5 to page 43, line 11 and Figure 20).

> Foulkes et al teach a process wherein the cells are derived from a clone (Claim 91).
>
> Foulkes et al teach a process wherein the target molecule is an intracellular component of a signal transmission pathway (Page 27, growth factor receptor).
>
> Foulkes et al teach a process wherein the target molecule is tyrosine kinase (Page 6, lines 1-6).
>
> Foulkes et al teach a process wherein the process is carried out in high throughput format with several dilutions of the substances (Page 60, line 10 to page 61, line 20).

(Office action, section 5, lines 4-20). Applicants respectfully disagree.

The screening methods of the present invention are directed to "a process for determining the pharmacological activity of a substance on the activity of different biological target molecules" (*see*, e.g., page 4, lines 15-17, and claim 1, at page 53, lines 4-6, of the application as filed). These target molecules are receptor proteins (*see, e.g.,* page 12, lines 21-30 of the application as filed). In contrast to the present invention, the screening methods disclosed by Foulkes *et al.* are methods "of determining whether a molecule not previously known to be a modulator of protein biosynthesis is capable of transcriptionally modulating the expression of a *gene encoding a growth factor*" (*see*, *e.g.,* page 32, lines 17-21, page 33, lines 12-16, page 34, lines 4-8, claim 71 at page 92, lines 3-7 and claim 72 at page 93, lines 93, lines 31-35) (emphasis added). Foulkes *et al.* does not teach screening for target molecules other than a molecule not previously known to be a modulator of protein biosynthesis which is capable of transcriptionally modulating the expression of a gene encoding a growth factor. Therefore, Foulkes *et al.* does not anticipate any of the pending claims.

Applicants respectfully submit that this rejection of claims 28-42, 44, 46, 49, 50, 53, 55, 56, and 58-60 under 35 U.S.C. § 102(b) has been overcome and should be withdrawn.

III. Rejection under 35 U.S.C. § 103

A. The First Rejection

The Examiner has rejected claims 28-42, 44, 46, 49, 50, 53, and 55-60 under 35 U.S.C. § 103(a) over Foulkes *et al.* in view of Chapman *et al.* (U.S. Patent 6,232,099 B1) (May 15, 2001). Office Action, section 7, lines 1-3. Applicants respectfully traverse this rejection.

The Examiner states that:

> Foulkes et al teach the process of claims 28-42, 44, 46, 49-50, 53, 55-56, and 58-60 as described above.
>
> Foulkes et al do not teach the Green fluorescent protein as the reporter gene.
>
> Chapman et al teach the Green fluorescent protein as the reporter gene (Examples 1 and 2 and Figures 1a and 1b).
>
> It would had been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the Green fluorescent protein of Chapman et al. in the process of Foulkes et al., since Chapman et al. state, "The green fluorescent protein (GFP) from A. Victoria is a reporter of gene expression in heterologous systems. GFP has an advantage over other marker proteins in that it can be detected non-invasively, without any requirement for exogenous substrates or co-factors since it fluoresces intrinsically without a requirement for exogenous substrate. In addition, fluorescence of GFP is retained in fusion proteins allowing the subcellular localization of fusion proteins (Column 7, line 66 to column 8, line 7)." An ordinary practitioner would have been motivated to combine and substitute the Green fluorescent protein of Chapman et al. in the process of Foulkes et al. in order to improve the process for determining the pharmacological effect of a substance on a cell and also in order to achieve

> the express advantages, as noted by Chapmen et al., of a protein which has an advantage over other marker proteins in that it can be detected non-invasively, without any requirement for exogenous substrates or co-factors since it fluoresces intrinsically without a requirement for exogenous substrate and in addition, fluorescence of which is retained in fusion proteins allowing the subcellular localization of fusion proteins.

Office Action, section 7, lines 4-24. Applicants respectfully disagree.

1. The Primary Reference: Foulkes et al.

The screening methods of the present invention are directed to "a process for determining the pharmacological activity of a substance on the activity of different biological target molecules" (*see*, e.g., page 4, lines 15-17, and claim 1, at page 53, lines 4-6, of the application as filed). These target molecules are receptor proteins (*see, e.g.*, page 12, lines 21-30 of the application as filed). In contrast to the present invention, the screening methods disclosed by Foulkes *et al.* are methods "of determining whether a molecule not previously known to be a modulator of protein biosynthesis is capable of transcriptionally modulating the expression of a *gene encoding a growth factor*" (*see, e.g.*, page 32, lines 17-21, page 33, lines 12-16, page 34, lines 4-8, claim 71 at page 92, lines 3-7 and claim 72 at page 93, lines 93, lines 31-35) (emphasis added).

The present invention claims a process for determining the pharmacological activity of a substance on the activity of different biological target molecules, wherein each of the biological target molecules is a receptor protein. In contrast to the present invention, Foulkes *et al.* does not teach or suggest screening for target molecules other than a molecule not previously known to be a modulator of protein biosynthesis which is capable of

transcriptionally modulating the expression of a gene encoding a growth factor. Therefore, claims 28-42, 44, 46, 49, 50, 53, and 55-60 are not obvious in view of Foulkes *et al.* The deficiencies in Foulkes *et al.* are not cured by the other references cited by the Examiner.

2. The Secondary Reference: Chapman et al.

"Chapman et al teach the Green fluorescent protein as the reporter gene (Examples 1 and 2 and Figures 1a and 1b)." Office Action, section 7, lines 7-8. Chapman *et al.* do not teach or suggest a process for determining the pharmacological activity of a substance on the activity of different biological target molecules, wherein each of the biological target molecules is a receptor protein. Thus, the deficiencies of Foulkes *et al.* are not cured by the teaching of Chapman *et al.* Therefore, claims 28-42, 44, 46, 49, 50, 53, and 55-60 are not obvious in view of Chapman *et al.* and the other references cited by the Examiner. Applicants respectfully submit that the rejection of claims 28-42, 44, 46, 49, 50, 53, and 55-60 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

B. The Second Rejection

The Examiner has rejected claims 28-44, 46, 49-51, 53, 55-56, and 58-60 under 35 U.S.C. § 103(a) over Foulkes *et al.* in view of Fodor *et al.* (U.S. Patent 6,309,822 B1) (October 30, 2001). Office Action, section 8, lines 1-3. Applicants respectfully traverse this rejection.

The Examiner states that

> Foulkes et al teach the process of claims 28-42, 44, 46, 49-50, 53, 55-56, and 58-60 as described above.
>
> Foulkes et al do not teach the receptor HER2 and Ras.
>
> Fodor et al teach the receptor HER2 and Ras. (Column 5, lines 44-62).
>
> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the receptors HER2 and Ras of Fodor et al. in the process of Foulkes et al., since Fodor et al. state, "Such genes include, but are not limited to the HER2 proto-oncogene in the case of breast cancer, receptor tyrosine kinases (RTKs) associated with the etiology of a number of tumors including carcinomas in the breast, liver, bladder, pancreas, as well as glioblastomas, sarcomas, and squamous carcinomas, and tumor suppressor genes such as the p53 gene and other "marker" genes such as RAS, MSH2, MLH1 and BRCA1 (Column 5, lines 48-55)". An ordinary practitioner would have been motivated to combine and substitute the receptors HER2 and Ras of Fodor et al. in the process fo Foulkes et al., in order to improve the process for determining the pharmacological effect of a substance on a cell and also in order to achieve the express advantages, as noted by Fodor et al., of receptors which are used as "marker" associated with the etiology of a number of tumors including carcinomas in the breast, liver, bladder, pancreas, as well as glioblastomas, sarcomas, and squamous carcinomas, and tumor suppressor genes.

Office Action, section 8, lines 4-21. Applicants respectfully disagree.

For the reasons stated in section III.A.1, above, claims 28-44, 46, 49-51, 53, 55, 56, and 58-60 are not obvious in view of Foulkes *et al.* Assuming *arguendo* that Fodor *et al.* teach the receptors HER2 and Ras and a potential utility for compounds that bind with the HER2 or the Ras receptor (*see* Office Action, section 8, lines 7-21), Fodor *et al.* do not teach or suggest screening, for compounds that bind with the HER2 or the Ras receptor, by the method of Foulkes *et al.* or by any other high-throughput methodology. Certainly, Fodor *et al.* do not teach or suggest a process for determining the pharmacological activity of a substance on the activity of different biological target molecules, wherein each of the biological target molecules is a receptor protein. Thus, the deficiencies of Foulkes *et al.* are

not cured by the teaching of Fodor *et al.* Therefore, claims 28-44, 46, 49-51, 53, 55, 56, and 58-60 are not obvious in view of Fodor *et al.* and the other references cited by the Examiner. Applicants respectfully submit that the rejection of claims 28-44, 46, 49-51, 53, 55, 56, and 58-60 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

C. The Third Rejection

The Examiner has rejected claims 28-42, 44-46, 49, 50, 53, 55, 56, and 58-60 under 35 U.S,.C. § 103(a) over Foulkes *et al.* in view of Bilodeau *et al.* (U.S. Patent 6,235,741 B1) (May 22, 2001). Office Action, section 9, lines 1-3. Applicants respectfully traverse this rejection.

The Examiner states that:

> Foulkes et al teach the process of claims 28-42, 44, 46, 49-50, 53, 55-56, and 58-60 as described above.
>
> Foulkes et al al do not teach the receptor KDR.
>
> Bilodeau et al teach the receptor KDR. (Column 2, lines 1-16).
>
> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the receptors KDR of Bilodeau et al. in the process of Foulkes et al., since Bilodeau et al. state, "Inhibition of KDR or Flt-1 is implicated in pathological neoangiogenesis, and these are useful in the treatment of diseases in which neoangiogenesis is part of the overall pathology, e.g., diabetic retinal vascularization, as well as various forms of cancer (Column 2, lines 12-16))". An ordinary practitioner would have been motivated to combine and substitute the receptors KDR of Bilodeau et al. in the process of Foulkes et al., in order to improve the process for determining the pharmacological effect of a substance on a cell and also in order to achieve the express advantages, as noted by Bilodeau et al., of KDR receptors which are implicated in pathological neoangiogenesis, and which are useful in the treatment of diseases in which neoangiogenesis is part of the overall

pathology, e.g., diabetic retinal vascularization, as well as various forms of cancer.

Office Action, section 9, lines 7-19. Applicants respectfully disagree.

For the reasons stated in section III.A.1, above, claims 28-42, 44-46, 49, 50, 53, 55, 56 and 58-60 are not obvious in view of Foulkes *et al.* Assuming *arguendo* that Bilodeau *et al.* teach receptor KDR and a potential utility for compounds that bind with receptor KDR, Bilodeau *et al.* does not teach or suggest screening, for compounds that bind with the receptor KDR, by the method of Foulkes *et al.* or by any other high-throughput methodology. Certainly, Bilodeau *et al.* do not teach or suggest a process for determining the pharmacological activity of a substance on the activity of different biological target molecules, wherein each of the biological target molecules is a receptor protein. Thus, the deficiencies of Foulkes *et al.* are not cured by the teaching of Fodor *et al.* Therefore, claims 28-42, 44-46, 49, 50, 53, 55, 56 and 58-60 are not obvious in view of Bilodeau *et al.* and the other references cited by the Examiner. Applicants respectfully submit that the rejection of claims 28-42, 44-46, 49, 50, 53, 55, 56 and 58-60 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

D. The Fourth Rejection

The Examiner has rejected claims 28-42, 44, 46, 47, 49, 50, 53, 55, 56, and 58-60 under 35 U.S.C. § 103(a) over Foulkes *et al.* in view of Nishi *et al.* (U.S. Patent 6,159,967)

(December 12, 2000). Office Action Section 10, lines 1-3. Applicants respectfully traverse this rejection.

The Examiner states that:

> Foulkes et al teach the process of claims 28-42, 44, 46, 49-50, 53, 55-56, and 58-60 as described above.
>
> Foulkes et al do not teach the neurokinin receptor. (Column 1, lines 30-40 and Column 244, line 65 to column 245, line 42).
>
> Nishi et al teach the neurokinin receptor. (Column 1, lines 30-40 and Column 244, line 65 to column 245, line 42).
>
> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the neurokinin receptor of Nishi et al. in the process of Foulkes et al., since Nishi et al. state, "The novel compounds of the present invention have a superior antagonistic effect on substance P and neurokinin receptors. Moreover since they have low toxicity, they are useful for the prevention and therapy of tachykinin-mediated diseases, examples of which include diseases of the central nervous system including anxiety, depression, psychosis and schizophrenia (Column 244, line 65 to column 245, line 5)". An ordinary practitioner would have been motivated to combine and substitute the neurokinin receptor of Nishi et al. in the process of Foulkes et al., in order to improve the process for determining the pharmacological effect of a substance on a cell and also in order to achieve the express advantages, as noted by Nishi et al., of neurokinin receptors which are implicated in diseases of the central nervous system including anxiety, depression, psychosis and schizophrenia.

Office Action, section 10, lines 4-20. Applicants respectfully disagree.

For the reasons stated in section III.A.1, above, claims 28-42, 44, 46, 47, 49, 50, 53, 55, 56 and 58-60 are not obvious in view of Foulkes *et al.* Assuming *arguendo* that Nishi *et al.* teach the neurokinin receptor and a potential utility for compounds that bind with the neurokinin receptor (*see* Office Action, section 10, lines 7-20, Nishi *et al.* do not teach or suggest screening for compounds that bind with the neurokinin receptor by the method of Foulkes *et al.* or by any other high-throughput methodology. Certainly, Nishi *et al.* do not

teach or suggest a process for determining the pharmacological activity of a substance on the activity of different biological target molecules, wherein each of the biological target molecules is a receptor protein. Thus, the deficiencies of Foulkes *et al.* are not cured by the teaching of Nishi *et al.* Therefore, claims 28-42, 44, 46, 47, 49, 50, 53, 55, 56 and 58-60 are not obvious in view of Nishi *et al.* and the other references cited by the Examiner. Applicants respectfully submit that the rejection of claims 28-42, 44, 46, 47, 49, 50, 53, 55, 56, and 58-60 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

E. The Fifth Rejection

The Examiner has rejected claims 28-42, 44, 46, 48-50, 53, 55, 56 and 58-60 under 35 U.S.C. § 103(a) over Foulkes *et al.* in view of Gerald *et al.* (U.S. Patent 6,331,401) (December 18, 2001). Office Action, section 11, lines 1-3. Applicants respectfully traverse this rejection.

The Examiner states that:

> Foulkes et al teach the process of claims 28-42, 44, 46, 49-50, 53, 55-56, and 58-60 as described above.
>
> Foulkes et al do not teach the serotonin receptor.
>
> Gerald et al teach the serotonin receptor. (Column 21, lines 16-50).
>
> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the serotonin receptor of Gerald et al. in the process of Foulkes et al., since Gerald et al. state, "Analysis of 5-HT4 structure and function provides a model for the development of drugs useful for the treatment of gastrointestinal conditions incuding bowel disease, postoperative ileus, diabetic gastroparesis, emesis, achalesia, hiatal hernia, and esophogal spasm (Column 21, lines 22-27)". An ordinary practitioner would have been

> motivated to combine and substitute the serotonin receptor of Gerald et al. in the process of Foulkes et al., in order to improve the process for determining the pharmacological effect of a substance on a cell and also in order to achieve the express advantages, as noted by Gerald et al., of serotonin receptors whose structure and function provides a model for the development of drugs useful for the treatment of gastrointestinal conditions including bowel disease, postoperative ileus, diabetic gastroparesis, emesis, achalesia, hiatal hernia, and esophagal spasm.

Office Action, section 11, lines 4-20. Applicants respectfully disagree.

For the reasons stated in section III.A.1, above, claims 28-42, 44, 46, 49, 50, 52, 53, 55, 56 and 58-60 are not obvious in view of Foulkes *et al.* Assuming *arguendo* that Gerald *et al.* do teach the serotonin receptor and a potential utility for compounds that bind with the serotonin receptor, Gerald *et al.* do not teach or suggest screening for compounds that bind with the serotonin receptor by the method of Foulkes *et al.* or by any other high-throughput methodology. Certainly, Gerald *et al.* do not teach or suggest a process for determining the pharmacological activity of a substance on the activity of different biological target molecules, wherein each of the biological target molecules is a receptor protein. Thus, the deficiencies of Foulkes *et al.* are not cured by the teaching of Gerald *et al.* Therefore, claims 28-42, 44, 46, 48-50, 53, 55, 56 and 58-60 are not obvious in view of Gerald *et al.* and the other references cited by the Examiner. Applicants respectfully submit that the rejection of claims 28-42, 44, 46, 48-50, 53, 55, 56 and 58-60 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

F. The Sixth Rejection

The Examiner has rejected claims 28-42, 44, 46, 49, 50, 52, 53, 55, 56 and 58-60 under 35 U.S.C. § 103(a) over Foulkes *et al.* in view of Johnson (U.S. Patent 6,331,170 B1) (December 25, 2001). Office Action, section 12, lines 1-3. Applicants respectfully traverse this rejection.

The Examiner states that:

> Foulkes et al teach the process of claims 28-42, 44, 46, 49-50, 53, 55-56, and 58-60 as described above.
>
> Foulkes et al do not teach the Raf receptor.
>
> Johnson teaches the Raf receptor. (Column 5, lines 11-18).
>
> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the Raf receptor of Johnson in the process of Foulkes et al., since Johnson states, "In particular, the method comprises regulating the apoptosis of the cell. Such a method is useful for the treatment of a medical disorder. In particular, the method is useful for inhibiting tumorigenesis and autoimmunity (Column 5, lines 14-18)". An ordinary practitioner would have been motivated to combine and substitute the Raf receptor of Johnson in the process of Foulkes et al., since[], in order to improve the process for determining the pharmacological effect of a substance on a cell and also in order to achieve the express advantages, as noted by Johnson, of Raf receptors useful for the treatment of a medical disorder and in particular useful for inhibiting tumorigenesis and autoimmunity.

Office Action, section 12, lines 4-17. Applicants respectfully disagree.

For the reasons stated in section III.A.1, above, claims 28-42, 44, 46, 49, 50, 52, 53, 55, 56 and 58-60 are not obvious in view of Foulkes *et al.* Assuming *arguendo* that Johnson. does teach the Raf receptor and a potential utility for compounds that bind to the Raf receptor (*see* Office Action, section 12, lines 7-17, Johnson does not teach or suggest screening, for

compounds that bind to the Raf receptor, by the method of Foulkes *et al.* or by any other high-throughput methodology. Certainly, Johnson. does not teach or suggest a process for determining the pharmacological activity of a substance on the activity of different biological target molecules, wherein each of the biological target molecules is a receptor protein. Thus, the deficiencies of Foulkes *et al.* are not cured by the teaching of Johnson. Therefore, claims 28-42, 44, 46, 49, 50, 52, 53, 55, 56 and 58-60 are not obvious in view of Johnson and the other references cited by the Examiner. Applicants respectfully submit that this rejection has been overcome and should be withdrawn.

G. The Seventh Rejection

The Examiner has rejected claims 28-42, 44, 46, 49, 50, 53-56 and 58-60 under 35 U.S.C. § 103(a) over Foulkes *et al.* in view of O'Hare *et al.* (U.S. Patent 6,017,735) (January 15, 2000). Office Action, section 13, lines 1-3. Applicants respectfully traverse this rejection.

The Examiner states that:

> Foulkes et al do not teach the bcl-2 receptor.
>
> O'Hare et al. teach the bcl-2 receptor. (Column 7, lines 4-8).
>
> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the bcl-2 receptor of O'Hare et al. in the process of Foulkes et al., since O'Hare et al. state, "Known proteins of the bcl2 family, such as bcl2 itself, bcl-XL, or bclw, to mask or inhibit apoptosis where this is desired, e.g., in treatment of neurodegeneration (Column 7, lines 5-8)". An ordinary practitioner would have been motivated to combine and substitute the bcl-2 receptor of O'Hare et al. in the process of Foulkes et al., in order to improve the process for determining the pharmacological effect of a substance on a cell and also in

> order to achieve the express advantages, as noted by O'Hare et al, of bcl-2 receptors useful to mask or inhibit apoptosis where this is desired, e.g., in treatment of neurodegeneration.

Office Action, section 13, lines 4-17. Applicants respectfully disagree.

For the reasons stated in section III.A.1, above, claims 28-42, 44, 46, 49, 50, 53-56 and 58-60 are not obvious in view of Foulkes *et al.* Assuming *arguendo* that O'Hare *et al.* do teach the bcl-2 receptor and a potential utility for compounds that bind to the bcl-2 receptor, O'Hare *et al.* do not suggest screening, for compounds that bind to the bcl-2 receptor, by the method of Foulkes *et al.* or by any other high-throughput methodology. Certainly, O'Hare *et al.* do not teach or suggest a process for determining the pharmacological activity of a substance on the activity of different biological target molecules, wherein each of the biological target molecules is a receptor protein. Thus, the deficiencies of Foulkes *et al.* are not cured by the teaching of O'Hare *et al.* Therefore, claims 28-42, 44, 46, 49, 50, 53-56 and 58-60 are not obvious in view of O'Hare *et al.* and the other references cited by the Examiner. Applicants respectfully submit that the rejection of claims 28-42, 44, 46, 49, 50, 53-56 and 58-60 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

IV. Response to Applicants' Previous Arguments

In response to Applicants' Amendment and Reply to the first Office Action on the merits of the above-captioned application, the Examiner states that "Applicant[s'] arguments filed on December 12, 2001 have been fully considered but they are not persuasive." Office

Action, section 15, lines 1-2. Applicants respectfully disagree with the Examiner's analysis and conclusion.

A. Rejection under 35 U.S.C. § 102(b)

The totality of the Examiner's argument, in support of rejection under 35 U.S.C. § 102(b), is as follows:

> In response to applicant's argument to withdraw the 102(b) rejection by mentioning that the Foulkes reference fail to show certain features of applicants[s'] invention, it is noted that the features upon which applicant relies (i.e., the target molecules are receptor proteins) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Office Action, section 15, lines 3-8. Applicants respectfully disagree.

In the interest of clarity, Applicants have amended independent claims 28-31 to specifically state that "each of said one or more biological target molecules is a receptor protein." Claims 32-60 are directly or dependent upon one or more of claims 28-31. Thus, none of pending claims is anticipated by the disclosure of Foulkes *et al.*

B. Rejection under 35 U.S.C. § 103(a)

The totality of the Examiner's argument, in support of rejection under 35 U.S.C. § 103(a), is as follows:

> In response to applicant[s'] arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Office Action, section 15, lines 9-12. Applicants respectfully disagree.

Contrary to the Examiner's assertion, Applicants have made a careful, well reasoned demonstration of the deficiencies in the primary reference previously cited by the Examiner (Foulkes *et al.*, PCT international Publication WO 92/13063) (*see* Amendment and Reply Under 37 C.F.R. § 1.111, filed December 21, 2001, page 18, line 1, through page 19, line 9). Applicants then clearly demonstrated that the deficiencies in Foulkes *et al.* were not cured by the secondary reference cited by the Examiner (Chapman *et al.*, U.S. Patent No. 6,232,099) (*see* Amendment and Reply Under 37 C.F.R. § 1.111, filed December 21, 2001, page 19, line 10, through page 20, line 20). Thus, Applicants have conclusively demonstrated that the Examiner has *not* established a *prima facie* case of obviousness.

In rebuttal, the Examiner has merely stated a proposition of law. The Examiner has not even attempted to demonstrate a connection between the proposition of law cited and the facts of this application. Thus, the Examiner has not made "a rebuttal of any arguments raised in the applicant's reply." *See* M.P.E.P. § 706.07 ("Statement of Grounds"). Therefore, Applicants respectfully submit that the finality of the present office action is premature and should be withdrawn.

V. Additional Matter

In the initial office action for the above-captioned application, the Examiner objected to claims 5-22 and 27 under 37 C.F.R. § 1.75(c) as being improper form because a multiple dependent claim cannot depend on another multiple dependent claim (*see*, File Wrapper

Paper No. 12, section 1). In the Amendment and Reply filed on December 21, 2001, (*see*, page 10, line 11, through page11, line 8) Applicants pointed out that the Examiner was incorrect because these multiple dependencies has been eliminated by a Preliminary Amendment that was filed with the Application on December 23, 1998.

Applicants specifically requested "that the Examiner issue a supplemental, non-final office action examining all pending claims including claims 37-54 and 59 which are directed to the subject matter of original claims 5-22 and 27 which were improperly objected to and thus not examined." In the present Office Action, the Examiner does not respond to this request. Therefore, the Examiner has improperly issued a final rejection after the first examination on the merits of pending claims 37-54 and 59. Applicants respectfully submit that the Examiner (a) allow all or the pending claims or (b) withdraw the finality of the pending Office Action, examine all of the pending claims on the merits thereof, issue a Supplementary Office Action, and establish a new statutory period for the submission of Applicants' Reply.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite

prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

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Version with markings to show changes made

In the Claims:

Claims 28-31 and 45 have been amended as follows:

28. (once amended) A process for determining the pharmacological effect of a substance on the activity of various biological target molecules, wherein a substance is applied to test cells which contain one or more biological target molecules and the effect of the substance on the activity of the target molecules is determined, characterised in that

(a) a defined amount of a test substance is applied to test cells with the same basic biological constitution which differ in that they contain one or more different biological target molecules;

(b) the effect of the substance on the or each biological target molecule is measured using a detection system coupled to the activation of the target molecule; and

(c) the effects measured in (b) are directly or indirectly compared with one another, whereby the effect of the substance on the activity of the target molecules is determined;

<u>wherein each of said one or more biological target molecules is a receptor protein, and</u>

wherein said test cells with the same basic biological constitution are test cells derived from one type of tissue and one species.

29. (once amended) A process for determining the pharmacological effect of a substance on the activity of various biological target molecules, wherein a substance is applied to test cells which contain one or more biological target molecules and the effect of the substance on the activity of the target molecules is determined, characterised in that

(a) a defined amount of a test substance is applied to test cells which contain one or more biological target molecules, the test cells differing in that they have different basic biological constitutions;

(b) the effect of the substance on the or each biological target molecule is measured using a detection system coupled to the activation of the target molecule; and

(c) the effects measured in (b) are directly or indirectly compared with one another, whereby the effect of the substance on the activity of the target molecules is determined;

wherein each of said one or more biological target molecules is a receptor protein, and wherein said test cells differing in that they have different basic biological constitutions are test cells not derived from one type of tissue and one species.

30. (once amended) A process for determining the pharmacological effect of a substance on the activity of various biological target molecules, wherein a substance is applied to test cells which contain one or more biological target molecules and the effect of the substance on the activity of the target molecules is determined, characterised in that

(a) a defined amount of a test substance is applied to test cells with the same basic biological constitution which differ in that they contain one or more different biological target molecules;

(b) the effect of the substance on different regulatory mechanisms triggered by the activation of the target molecules is determined by measuring the effect using a plurality of detection systems each coupled to the different regulatory mechanisms; and

(c) the effects of the test substance on the different test cells or the effects determined using different detection methods are directly or indirectly compared with one another, whereby the effect of the substance on the activity of the target molecules is determined;

wherein each of said one or more biological target molecules is a receptor protein, and wherein said test cells with the same basic biological constitution are test cells derived from one type of tissue and one species.

31. (once amended) A process for determining the pharmacological effect of a substance on the activity of various biological target molecules, wherein a substance is applied to test cells which contain one or more biological target molecules and the effect of the substance on the activity of the target molecules is determined, characterised in that

(a) a defined amount of a test substance is applied to test cells which contain one or more biological target molecules, the test cells differing in that they have different basic biological constitutions;

(b) the effect of the substance on different regulatory mechanisms triggered by the activation of the target molecules is determined by measuring the effect using a plurality of detection systems each coupled to the different regulatory mechanisms; and

(c) the effects of the test substance on the different test cells or the effects determined using different detection methods are directly or indirectly compared with one another, whereby the effect of the substance on the activity of the target molecules is determined;

wherein each of said one or more biological target molecules is a receptor protein, and

wherein said test cells differing in that they have different basic biological constitutions are test cells not derived from one type of tissue and one species.

45. (once amended) The process of claim 41, wherein the [receipt] receptor is KDR.